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Boric acid: an efficient and environmentally benign catalyst for transesterification of ethyl acetoacetate☆

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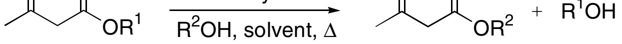
Abstract—An efficient and environmentally benign boric acid catalyzed protocol for the transesterification of ethyl acetoacetate with a variety of primary and secondary alcohols in good to excellent yields is described. The versatility of this transformation is demonstrated with problematic substrates such as propargyl alcohol and allyl alcohol, which are known to undergo Carroll rearrangement during transesterification.

β-Keto esters are valuable synthons in organic synthesis since their electrophilic and nucleophilic sites allow their derivatization to complex natural products.[1] Typically, β-keto esters are prepared by decomposing highly reactive and unstable diketene with various alcohols.[2,3] Although this methodology is atom economic, the corrosiveness and handling difficulties of diketene make it practically less attractive. A few alternative methods have been developed,[4–8] in particular, transesterification[9] of β-keto esters to other β-keto ester analogs (Scheme 1). Since transesterification is an equilibrium process, an acidic or basic catalyst is required to promote the reaction. In this regard, several protic acid[10–13] and basic catalysts[14–20] have been reported in the literature to effect this transformation. The limitation of using protic acids or basic catalysts is that acid or base sensitive substrates are not compatible under these reaction conditions. To overcome this problem, Lewis acid catalyzed transesterifications have been developed, using Lewis acids such as distannoxanes,[21] indium triiodide,[22] yttria–zirconia,[23] Mo–ZrO_2,[24] $LiClO_4$,[25] Zn dust,[26] titanium(IV) alkoxides,[27] zinc–I_2,[28] sodium perborate[29] and niobium(V) oxide.[30] A few other homogeneous[31,32] and heterogeneous[33–37] catalysts are also known to be effective for this transformation. However, some of these catalysts are toxic, difficult to prepare and are expensive.



Scheme 1. General transesterification process.

In recent years, there has been considerable interest in developing Green Chemistry[38] for organic synthesis due to environmental demands and sustainability. The development of catalytic processes to replace stoichiometric reactions, which produce large amounts of waste by-products, has made a significant contribution to the reduction of environmental pollution. With this in mind, we have developed the transesterification of ethyl acetoacetate using boric acid as a catalyst. Boric acid is an environmentally benign catalyst, which has been successfully utilized in numerous reactions.[39–41] Though boric acid catalyzed esterification of α-hydroxy acids[42] and phenols[43] is known, transesterification of β-keto esters using this catalyst, to the best of our knowledge, has not been reported in the literature.

To prove the catalytic activity of boric acid in transesterification reactions, we initially conducted a blank

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Keywords: Transesterification; β-Keto esters; Boric acid; Green catalysis.

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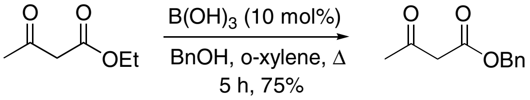
reaction, in which ethyl acetoacetate **1** was reacted with 2 equiv of benzyl alcohol in xylene at reflux without boric acid. The desired benzyl ester was obtained in only trace amounts even after 24 h. When the same reaction was conducted using 1.5 equiv of benzyl alcohol and 10 mol % of boric acid at reflux, β-keto ester **2** was obtained in 75% yield within 5 h (Scheme 2).

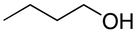
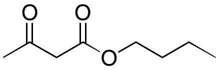
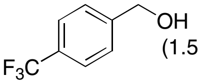
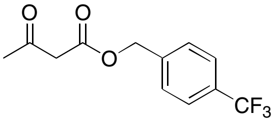
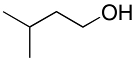
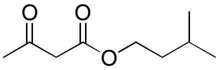
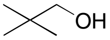
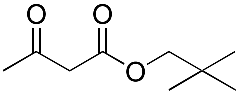
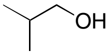
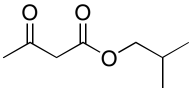
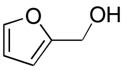
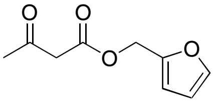
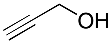
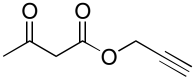
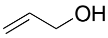
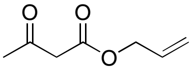
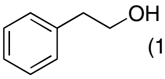
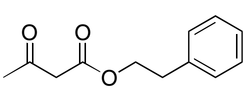
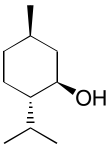
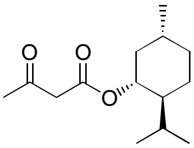
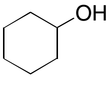
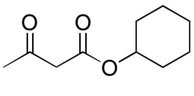
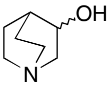
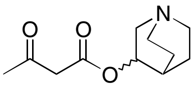
To demonstrate the scope of this methodology, a wide variety of aliphatic alcohols were reacted with ethyl acetoacetate using 10 mol % of boric acid in refluxing toluene[44] and the results are summarized in Table 1. In all these experiments ethanol was continuously removed from the reaction mixture using a Dean–Stark condenser.



1 **2**

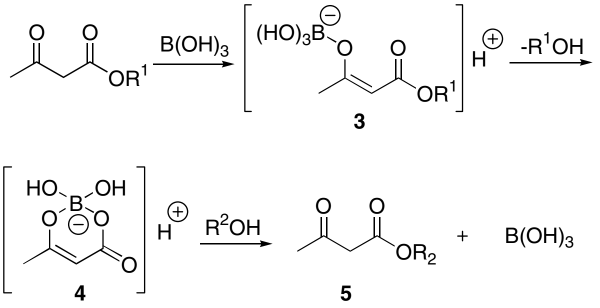
Scheme 2. Boric acid catalyzed transesterification of ethyl acetoacetate.

Table 1. $B(OH)_3$ catalyzed transesterification of ethyl acetoacetate with alcohols[a]

S. No.	Alcohol (equiv)	Product	Yield[b] (%)
1	 (2)		92
2	 (1.5)		95
3	 (2)		82
4	 (2)		80
5	 (2)		72
6	 (2)		72
7	 (2)		71
8	 (2)		69
9	 (1.5)		77
10	 (1.5)		92
11	 (2)		95
12	 (1.5)		92

[a] All reactions were carried out with 10 mol % of $B(OH)_3$ in refluxing toluene for 5 h.

[b] All compounds showed satisfactory ^1H NMR and mass spectral data.



Scheme 3. Possible mechanism for the boric acid catalyzed transesterification.

Under optimized reaction conditions, transesterification of ethyl acetoacetate proceeded very cleanly. It is apparent from Table 1 that a variety of primary (entries 1–9) and secondary (entries 10–12) alcohols could be converted to their corresponding β-keto esters in good yields. In most cases 2 equiv of alcohol was used, in some cases 1.5 equiv of alcohol was found to be sufficient. A remarkable feature of this protocol is that substituted benzyl, propargyl and allyl alcohols (entries 2, 7, and 8) underwent transesterification efficiently with ethyl acetoacetate to provide the corresponding β-keto esters. Allyl and propargyl esters are known to be very difficult to prepare as they readily undergo the Carroll rearrangement.[45,46] Secondary alcohols such as (−)-menthol, cyclohexanol and quinuclidinol[47] (entries 10–12) were also transesterified smoothly under these conditions. Tertiary alcohols did not undergo the transesterification reaction even under drastic conditions.

A plausible mechanism is shown in Scheme 3. Probably, boric acid catalyzes the enolization of the β-keto ester to form intermediate **3**, which could then be converted to the cyclic intermediate **4**. Nucleophilic ring opening of the cyclic intermediate **4** by the alcohol gives the product along with the elimination of boric acid.

In conclusion, we have developed an efficient and cost effective protocol for the transesterification of ethyl acetoacetate using boric acid as an environmentally benign catalyst. We have also shown the versatility of this transformation by applying this method to a wide variety of alcohols.

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44. Except for benzyl alcohol, all the other primary and secondary alcohols examined underwent transesterification smoothly with ethyl acetoacetate in refluxing toluene. Since, in the case of benzyl alcohol, the transesterification reaction in toluene took a very long time, it was replaced with *o*-xylene (Scheme 2).
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47. In a typical experimental procedure, a mixture of ethyl acetoacetate (1.30 g, 10.0 mmol), quinuclidinol (1.90 g, 15.0 mmol) and boric acid (60 mg, 10 mol %) in toluene (50 mL) was refluxed for 5 h with continuous removal of ethanol using a Dean–Stark condenser. The solvent was removed under reduced pressure and the crude material was subjected to column chromatography on silica gel to give pure product. Data for quinuclidinyl acetoacetate (Table 1, entry 12) (92% yield, 1.94 g). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.21–1.38 (m, 1H), 1.49–1.55 (m, 1H), 1.61–1.68 (m, 1H), 1.74–1.79 (m, 1H), 2.24 (s, 3H), 2.64–2.83 (m, 6H), 3.19 (ddd, $J = 14.8, 8.4, 1.6$ Hz, 1H), 3.44 (s, 2H), 4.79–4.83 (m, 1H); MS (ESI): 212 (M+1).